

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
PIPERALIN

Chemical Code # 000488, Tolerance # 50024

SB 950 # 322

Original date: June 10, 2003

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, inadequate study.
Chronic toxicity, dog:	Data gap, inadequate study.
Oncogenicity, rat:	Data gap, no study on file.
Oncogenicity, mouse:	Data gap, no study on file.
Reproduction, rat:	Data gap, inadequate study.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	Data gap, no study on file.
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	Data gap, inadequate study, no adverse effect indicated.
DNA damage:	Data gap, inadequate study, no adverse effect indicated.
Neurotoxicity:	Not required at this time.

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Toxicology one-liners are attached.

All record numbers through 141618 were examined.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T030610

Original: J. Kishiyama and Gee, 6/10/03

The US EPA issued a "Reregistration Eligibility Decision (RED)" in September of 1994. In 1994, US EPA was requiring an additional *in vivo* cytogenetics study. All other required areas of toxicity had adequate studies. There is one product currently registered in California with non-food uses.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### CHRONIC TOXICITY, RAT

002 022084 "Chronic Toxicity of EL-211." (Eli Lilly and Co. Lilly Research Laboratories, December 8, 1963.) Piperalin was admixed with the diet at concentrations of 0, 500, 1000 or 2000 ppm and fed to 25 rats/sex/group. No abnormalities reported. NOEL = 2000 ppm. UNACCEPTABLE (major variances, insufficient information for assessment). (D Shimer and J. Remsen, 8/22/85).

### CHRONIC TOXICITY, DOG

002 034852 "Dog study D19-63." (Eli Lilly and Co. Lilly Research Laboratories, December 19, 1963.) Piperalin was administered via gelatin capsule at levels of 0, 500, 1000 or 2000 ppm to 3 dogs/sex/group during the 244-day study. No adverse effects reported. NOEL stated as 2000 ppm. UNACCEPTABLE (not a chronic study, major variances, insufficient information. (D. Shimer and J. Remsen; 8/22/85).

### ONCOGENICITY, RAT

No study submitted.

### ONCOGENICITY, MOUSE

No study submitted.

### REPRODUCTION, RAT

002 022085 "Rat Reproduction Study R0223." (Eli Lilly and Co. Lilly Research Laboratories, December 16, 1963.) Piperalin was admixed with the diet at concentrations of 0, 500 or 1000 ppm and fed to 10 male and 20 female rats/group. No adverse effects reported for F<sub>0</sub> and F<sub>1</sub> pups. Reported NOEL = 1000 ppm. UNACCEPTABLE (major variances, insufficient information for assessment). (D. Shimer and J. Remsen; 8/22/85).

### TERATOLOGY, RAT

\*\* 007 067338 Negilski, D. S. and S. L. Liu. "Teratology Study of Piperalin (EL-211, Compound 038648) Administered Orally to CD Rats." (Lilly Research Laboratories, Laboratory Project Identification: R13487, March 23, 1988.) Piperalin (lot 086KE7, purity 99.0%) was administered via a single gavage/day during gestation days 6-15 at doses of 0 (10% aqueous acacia), 20, 100, and 500 mg/kg/day to 25 Sprague-Dawley mated female rats/group. Excessive salivation was noted at 100 and 500 mg/kg/day in dams and lower bodyweight gain and food consumption at 500 mg/kg/day. Maternal NOEL = 20 mg/kg/day. Fetal bodyweight was lower at the high dose by 5 - 6%. Developmental NOEL = 100 mg/kg/day. There was no evidence of

teratogenicity. ACCEPTABLE. (Kishiyama and Gee, 6/10/03).

## TERATOLOGY, RABBIT

No study submitted.

## GENE MUTATION

\*\* 019 114724 Negilski, D. S., T. J. Oberly, B. J. Bewsey and G. S. Probst. "The Effect of Preplan on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells." (Lilly Research Laboratories, Laboratory Project Identifications: 870513MLT2967, 870527MLA2967, and 870603MLA2967, September 23, 1987.) Piperalin (lot 086KE7, purity 99.0%) was tested at concentrations ranging from 1 to 100 µg/ml and 1 to 40 µg/ml without and with metabolic activation, respectively, with mouse lymphoma cells. There were triplicate plates for mutation frequency determination. There was a single trial without activation and two trials with activation, due to the toxicity of piperalin in the first trial. There was no increase in mutation frequency with piperalin at the concentrations tested. The positive controls were functional. ACCEPTABLE. (Kishiyama and Gee, 6/9/03).

\*\* 019 114729 Negilski, D. S., M. A. Rexroat, and G. S. Probst. "The Effect of Piperalin on the Induction of Reverse Mutation in *Salmonella typhimurium* and *Escherichia coli* Using the Ames Test." (Lilly Research Laboratories, Laboratory Project Identification: 870420AMT2967 and 870427AMS2967, September 9, 1987.) Piperalin (lot 086KE7, purity 99.0%) was tested at concentrations ranging from 62.5 to 1000 ug/plate without and at 250 to 4000 ug/plate with Aroclor 1254 induced rat liver metabolic activation, with *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2uvrA<sup>-</sup>. There were triplicate plates in a single trial. Toxicity was noted at the higher concentrations. No increase in the number of *S. typhimurium* and *E. coli* revertants with piperalin treatments with and without metabolic activation was reported. ACCEPTABLE (some deficiencies). (Kishiyama and Gee, 6/9/03).

## CHROMOSOME EFFECTS

019 114722 Negilski, D. S., J. D. Brunny and G. S. Probst. "The Effect of Piperalin on the *In Vivo* Induction of Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters." (Lilly Research Laboratories, Laboratory Project Identification: 870518SCE2967, October 14, 1987.) Piperalin, purity 99.0% ai, was administered in a single gavage, at doses of 0 (corn oil), 125, 250, or 500 mg/kg to 3 female Chinese hamsters/group. Animals were sacrificed 21 hours after treatment. Twenty-five cells were scored per slide. The frequency of SCE formation with piperalin treatment was not significantly increased. The positive control (cyclophosphamide) was functional. UNACCEPTABLE (too few females, no justification for using one sex only, no analysis of dosing material). (Kishiyama and Gee, 6/9/03).

## DNA DAMAGE

019 114723 Negilski, D. S., L. E. Hill, and G. S. Probst. "The Effect of Piperalin on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes." (Lilly Research Laboratories, Laboratory Project Identification: 870428UDS2967 and 870505UDS2967, September 9, 1987.) Piperalin (purity 99.0%, lot 086KE7) was tested at

concentrations (0.5 to 1000 µg/ml) with primary rat hepatocytes for the induction of UDS in two assays. Twenty cells were scored per concentration. No piperalin induced UDS in cultured rat hepatocytes. Positive controls were functional. UNACCEPTABLE (summary data only). Upgradeable. (Kishiyama and Gee, 6/9/03).

## OTHER

### Subchronic:

026 141620 Negilski, D. S., C. S. Van Pelt, and T. L. Torrence. "Subchronic (21-Day) Dermal Toxicity Study in New Zealand White Rabbits with Technical Piperalin." (Lilly Research Laboratories, Laboratory Project Identification: B01987, January 13, 1988.) Piperalin (purity 99.0%, density of 1.17 g/ml) was administered for 6 hours to the skin of the backs (clipped of fur) of 5 New Zealand rabbits/sex/group at concentrations of 0 (sesame oil), 4.3%, 12.8%, or 38.5%. The treatment was once daily for 21 consecutive days. These concentrations were equivalent to 0, 50, 150 and 450 mg/kg/day. Satellite (high dose and control) reversibility groups were included. Incidence and severity of skin thickening (acanthosis, hyperkeratosis, parakeratosis) of the application site was dose related for piperalin treatments. The satellite group indicated the skin thickening effect of piperalin was reversible. There were no treatment-related toxicological effects on ophthalmology, body weight, food consumption, hematology or histopathology (other than skin). UNACCEPTABLE. No analysis or data to confirm homogeneity, stability and content of dosing material. Upgradeable. No adverse systemic effect. (Kishiyama and Gee, 6/6/03).

### Acute:

\*\* 025 141616 G. E. Brown, Negilski, D. S. and T. F. Markey. "The Acute Oral, Dermal and Inhalation Toxicity and Primary Dermal Irritation of Technical Piperalin." (Lilly Research Laboratories, Laboratory Project Identification: R-O-78-87, R-O-79-87, B-D-56-87 and R-H-014-87, October 14, 1987.) Piperalin (purity 99.0%, density of 1.17 g/ml) was administered (one-time/animal/study) orally at doses of 500, 1100, 2500, or 5000 mg/kg to 5 Fischer 344 rats/sex/group. Acute Oral LD<sub>50</sub> = 1419 mg/kg for males and 800 mg/kg for females - III. For acute dermal toxicity, 5.0 ml of technical piperalin/kg was applied to the skin of 5 New Zealand white rabbits/sex. Acute Dermal LD<sub>50</sub> >5.0 ml/kg - IV. Piperalin was given by inhalation (nose only) at 0.584 and 5.040 mg/L to 5 Fischer 344 rats/sex/group. Acute Inhalation LC<sub>50</sub> <5.040 mg/L of air but >0.584 mg/L of air - III. All animals died during exposure at the higher dose. ACCEPTABLE (Kishiyama and Gee, 6/6/03).

### Acute:

\*\* 025 141618 Negilski, D. S., G. L. Rock and D. E. Weaver. "The Acute Ocular Irritation of Piperalin (EL-211, Compound 038648) in the New Zealand White Rabbit." (Lilly Research Laboratories, Laboratory Project Identification B02290, May 25, 1990.) Piperalin technical (lot 086-KE7, 101.8% purity, density of 1.17g/ml) was administered at 0.1 ml to one eye of 3 New Zealand rabbits/sex. Corneal dullness, iritis, and conjunctivitis were noted within 24 hours but cleared within 7 days after treatment. Category III. ACCEPTABLE acute study. (Kishiyama

and Gee, 6/9/03)